## Remarks

Status of the Claims

All pending claims have been cancelled, and new Claims 161-163 are added through this amendment. The new claims place the application in condition for allowance or, alternatively, in better position for appeal. Basis for the new claims can be found in at least the following places:

Originally filed claims 1, 2, and 6-8
Page 1, lines 15-18
Page 3, line 14
Page 6, lines 13-20
Page 8, line 32 through page 9, line 2
Page 13, lines 14-19
Page 31, line 6 through page 32, line 5
Page 33, lines 26-31
Page 35, lines 8-10
Examples 6, 7, and 9-13

Rejection of Claims 159 and 160 under 35 U.S.C. § 103

A. Rejection

Claims 159 and 160 stand "rejected under 35 U.S.C. § 103(a) as being unpatentable over Keene *et al.*, The Journal of Biological Chemistry Vol. 264/9: 4769-4775 (1989) in view of Skrabanja *et al.*, EP 0853 945 A1 . . . and Andya *et al.*, US Patent No. 6,267,958 B1 . . . ." Because this amendment cancels Claims 159-160 and adds Claims 161-163, the remarks herein will address the patentability of Claims 161-163 over the abovementioned art, cited by the Examiner.

B. Level of Skill in the Art

The level of skill in the art is described to a great extent by the declarations of Dr. DeFelippis and Dr. Beals. Highly purified proteins were known to be unstable in solution, and thus were usually provided in lyophilized form for reconstitution. *See* Beals, para. 76. FSH, a non-covalently bonded heterodimer, was known to be unstable; consequently FSH products were marketed for decades as a lyophilized powder to be reconstituted before injection. *See* Beals, para. 75. According to Skrabanja:

> The stability of proteins in aqueous formulations is generally a problem in pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions.

Skrabanja, p. 2, ll. 42-45.

Several different attempts have been made to provide a stable FSH solution, such as adding saccharides, antioxidants (e.g., methionine), and even covalently bonding the α and β chains of FSH to form a single chain protein. *See* Beals, para. 76. Although these attempts yielded improved formulations, none taught or suggested any antimicrobial preservative—with one exception: Donaldson *et al.* (Donaldson, U.S. Patent No. 5,162,306).

Donaldson describes an FSH formulation comprising a particular ratio of FSH and LH for superovulation in mammals. Donaldson notes: "The present invention is also directed to a method for producing superovulation, out of season breeding and twinning in mammals. The method of the present invention comprises administering to cattle, sheep, goats, domestic and exotic mammals, the composition of the present invention." (col. 6, lines 3-8). Significantly, Donaldson notes the following with regard to preservative compatibility:

> Food and Drug Administration regulations require that any multidose injectable use a preservative for the prevention of bacterial contamination of the multidose vial. On page 1491 of the U.S.P. XXI (Pharmaceutic Ingredients/Reference Tables) as listed by categories under the heading of Antimicrobial Preservative is listed Thymol along with other preservative materials. ***Thymol was found to be one in the list of the preservatives that does not damage glycoprotein hormones.*** In order to prove that Thymol can be used with the superovulation compound of the present invention as a preservative, it was established that 0.1% weight of Thymol does not harm FSH. A phosphate buffered saline was used as the diluent but other solutions such as normal saline would be safe to use. U.S.P. XXI, NF XVI Antimicrobial Preservative effectiveness tests were completed utilizing two levels of Thymol (0.08% and 0.04% by weight) against superovulation composition with diluent. Thymol at the 0.08% by weight was effective against all the test organisms and the 0.04% by weight was effective against four out of five.
>
> Preservatives are substances added to dosage forms to protect them from microbial contamination. They are required to be added to multidose vials. ***Of the 24 antimicrobial preservatives listed on Page 1491 of U.S.P. XX 1, and U.S.P. and NF Pharmaceutical Ingredients, Thymol (5-methyl-2(1-methylethyl) phenol) was found to be compatible with FSH.*** Thymol is only slightly soluble in water, e.g., at 19.degree. C. 1.3 g/liter and at 100.degree. C. 1.6 gm/liter. Thus a useful working solution at room temperature is a 1% solution. It was therefore decided to test the compatibility of 1% Thymol in phosphate buffered saline on the activity of FSH over a period of four days, the recommended life of a multidose vial of SUPER-OV solution.

> SUPER-OV is a follicle stimulating hormone preparation that is used in inducing superovulation in mammals prior to estrus induction and subsequent insemination, embryo collection and transfer.
>
> The purpose of this study was to evaluate the effects of 1% Thymol on the integrity of the biological activity of FSH when used in SUPER-OV DILUENT is used to dissolve SUPER-OV for use in divided doses over a four day period. The objective was to define the FSH activity of SUPER-OV after being in a solution of PBS or PBS and 1% Thymol for four days. PBS was made up to make a solution containing Sodium chloride 8%, Potassium chloride 0.02%, Potassium phosphate 0.02% and Sodium phosphate 0.102%. One vial each containing 75 units of FSH were used.
>
> • • •
>
> PBS or PBS containing 1% Thymol does not effect the FSH activity of SUPER-OV over a four day period making 1% Thymol a potential preservative for use in SUPER-OV DILUENT.

(emphasis added) Donaldson, col. 25, l. 40 through col. 26, l. 22; and col. 27, l. 67 through col. 28, l. 2.

Donaldson's product, SUPER-OV®, was approved by the FDA for superovulation in cows, a veterinary indication. The product is sold as a lyophilized powder that is reconstituted with a diluent. (http://www.fda.gov/cvm/efoi/section2/140014081393.html). The reconstituted solution may be used over a period of 3 days. Thus, Donaldson acknowledges (1) that preservatives were known to damage glycoproteins, and (2) specifically teaches that thymol was the only preservative that provided sufficient stability to the described '306 formulations for up to 4 days. Donaldson conveys to the person of skill in the art that preservatives, other than thymol, damage FSH and cause instability of the product.

Other teachings, in addition to Donaldson, indicate to the skilled person that the addition of antimicrobial preservatives to a liquid protein formulation often destabilizes the protein. *See* DeFelippis, para. 8. Preservatives such as phenol, m-cresol, and benzyl alcohol have been shown to cause degradation of several proteins, including human growth hormone, interferon-gamma, and insulin-like growth factor. *See* Maa and Hsu, *Intl. J. Pharm.* 140:155-58 (1996), reference CBU; Lam *et al.*, *Pharm. Res.* 14(6):725-29 (1997), reference CAC; Remmele *et al.*, *Pharm. Res.* 15(2):200-08 (1998), reference CAA; Fransson *et al.*, *Pharm. Res.* 14(5):606-12 (1997), reference CAB; and Akers, *J. Pharm. Sci.* 91(11):2283-2300 (2002), reference CBW. The effect is unpredictable, and depends on the protein, preservative, and other excipients selected. Extensive experimentation is necessary to determine if a stable formulation can be achieved. *See*

DeFelippis, para. 12-13. The selection of each component is by no means "routine" or obvious. No single preservative works for all proteins.

C. Scope and Content of the Prior Art and Differences Between the Claimed Invention and the Prior Art

The prior art cited by the Examiner, when combined, does not make the instant invention obvious. To illustrate this point, I will discuss each reference individually, then in combination, and compare the combination to the instant invention.

Keene

Keene *et al.* ("Keene") provide the sequence of human FSH and how to express it recombinantly. Keene does not teach, suggest, or motivate a person of skill in the art to make any formulation of FSH.

Skrabanja

Skrabanja et al. ("Skrabanja") describes problems associated with the stability of FSH, indicating that this instability led to FSH being supplied as a lyophilized product that must be reconstituted. Skrabanja notes:

> **The stability of proteins in aqueous formulations is generally a problem in pharmaceutical industry. Likewise the stability of aqueous solutions of the gonadotropins is insufficient to allow storage for longer times. This is especially true for preparations containing the very pure gonadotropins, prepared using recombinant DNA methods, in relatively dilute solutions.** Usually therefore those preparations are stored in a dry form, as is obtained after lyophilization. A stabilized gonadotropin containing lyophilized pharmaceutical formulation is disclosed in European Patent No. 448,146 (Akzo N. V.). These preparations contain organic carboxylic acids, particularly citric acid, and optionally a non-reducing sugar such as sucrose. Another solid gonadotropin containing pharmaceutical composition comprising sucrose as a stabilizer is disclosed in the International Patent Application WO 93/11788 (Applied Research Systems ARS Holding N.V.).
>
> Although these freeze-dried preparations are stable enough to guarantee sufficient shelf-lifes, they have the disadvantage that prior to administration reconstitution is necessary. The patient therefore necessarily has to reconstitute the dried glycoprotein in a solvent before use, which is a disadvantage and an inconvenience to the patient. In addition, the solvent must be provided together with the freeze-dried preparation of the gonadotropin.
>
> For a patient, who needs injections of a gonadotropin at regular times, for instance a patient receiving a daily dose of recFSH for ovulation

> induction, it would be of importance that the gonadotropin formulation is easy to handle, to dose and to inject. The reconstitution of a freeze-dried gonadotropin preparation demands prudence and carefulness and should be avoided if possible. It would facilitate the use of gonadotropins, if these glycoproteins could be produced and distributed as a stable solution to the patient, who could inject the medicament directly without reconstitution. In addition, a freeze-drying process is a costly and time consuming process step, and it would be an advantage if this step could be avoided when preparing a gonadotropin formulation.

(Emphasis added)

Skrabanja provides improved formulations of a liquid gonadotropin formulation with a stabilizing amount of a polycarboxylic acid or a salt thereof and a thioether compound. The teaching of Skrabanja is comprehensive, leaving little doubt to the excipients contemplated and disclosed. The specification describes the claimed excipients (the carboxylic acids and thioether compounds), optional excipients (non-reducing sugars such as sucrose or trehalose and non-ionic surfactants) and is complete in its teaching. For example, page 4, lines 23 through 33, Skrabanja sets out nonionic surfactants such as Polysorbate 20, Polysorbate 80, Brij 35, or Pluronic F123 as an optional and preferred embodiment. Also, on page 4, lines 46 to 48, Skrabanja specifies the water to be used and even notes that a water miscible solvent may be present as a co-solvent.

The examples of Skrabanja are similarly complete, specifying the identity and amount of each and every excipient, including the q.s. volume (the total volume of the sample after water was added), indicating that no other excipients are present in the formulation. No antimicrobial preservatives, such as phenol, m-cresol, p-cresol, and o-cresol, are included in the examples. The examples measure the "retainment of in-vitro bioactivity of FSH compositions" (*i.e.*, the stability) over two months at four different temperatures. The samples were stored in closed 2 mL vials ("cartridge" is defined to include vials (page 5, line 23)). These examples were designed to demonstrate, and did demonstrate, that formulations without methionine were less stable than those with methionine. Nonetheless, Skrabanja's stable formulation, in a "cartridge for multiple uses," **did not contain** an antimicrobial preservative such as phenol, m-cresol, p-cresol, o-cresol, or mixtures thereof. **Skrabanja is so complete in its teaching that the reference lacks the necessary suggestion or motivation to add any unnamed excipient.**

In context, Skrabanja's use of the term "multiple use" **does not necessarily mean**

**that the product is preserved**. See Plouffe, para. 8-9. For example, according to the "Note for Guidance on Maximum Shelf-life for Sterile Products for Human Use After First Opening or Following Reconstitution," an **unpreserved, sterile product may be used multiple times so long as the in-use stability has been established**. *See* EUROPEAN AGENCY FOR THE EVALUATION OF MEDICINAL PRODUCTS, COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP), Guidance CPMP/QWP/159/96, 1999, emphasis added, reference CCC. Typically, the unpreserved product would not be used for more than 24 hours when stored at 2-8°C, unless reconstitution or dilution occurred under controlled and validated aseptic conditions. *Id.* Within this 24-hour period, a formulation may be administered multiple times, thus making it "multiple use." Hence, Skrabanja fails to disclose or teach the presently claimed invention. Furthermore, in view of complete teaching of Skrabanja (particularly in view of Donaldson, which expressly suggests preservatives other than thymol are incompatible), there is simply no motivation to combine Skrabanja with Andya or other reference that generally teach the use of phenol, m-cresol, p-cresol, o-cresol, or mixtures thereof. The specific teaching of Skrabanja and Donaldson clearly point the reader from such combinations.

Andya

Andya *et al.* (Andya) provides a stable lyophilized formulation that can be reconstituted with a diluent containing a preservative to generate a multi-use formulation with high protein concentration. Andya also describes an improvement—the addition of certain excipients, namely lyoprotectant such as sucrose or trehalose—such that the lyophilized protein formulations are stable upon storage. The formulations are stable as a solid, freeze-dried powder. Andya also notes that upon reconstitution the formulation is stable "for at least the time over which it will be administered to a patient." Andya, col. 1, ll. 55-59. Thus, Andya describes certain lyoprotectants that provide stability to freeze dried protein formulations but also teaches to limit the use of the reconstituted protein to the period of time over which the protein is administered to the patient (a period generally shorter than the shelf-life required to manufacture, distribute, store, and finally administer a solution).

The object of Andya is to provide a lyophilized formulation that, when reconstituted, provides a very high protein concentration. In fact, Andya requires a concentration greater than or equal to 50 mg protein/mL diluent (a range of >25

times the claimed protein concentration). It does not teach or suggest that a lower concentration protein formulation would be stable.

Andya provides an extensive list of more than 100 proteins that may be used in the lyophilized formulation.

> Examples of proteins encompassed within the definition herein include mammalian proteins, such as, e.g, growth hormone, including human growth hormone and bovine growth hormone; growth hormone releasing factor; parathyroid hormone; thyroid stimulating hormone; lipoproteins; α-1 -antitrypsin; insulin A-chain; insulin B-chain; proinsulin; follicle stimulating hormone; calcitonin; luteinizing hormone; glucagon; clotting factors such as factor VIIIC, factor , tissue factor, and von Willebrands factor; anti-clotting factors such as Protein C; atrial natriuretic factor; lung surfactant; a plasminogen activator, such as urokinase or tissue-type plasminogen activator (t-PA); bombazine; thrombin; tumor necrosis factor-α and -β; enkephalinase; RANTES (regulated on activation normally T-cell expressed and secreted); human macrophage inflammatory protein (MIP-1-α); serum albumin such as human serum albumin; mullerian-inhibiting substance; relaxin A-chain; relaxin B-chain; prorelaxin; mouse gonadotropin-associated peptide; DNase; inhibin; activin; vascular endothelial growth factor (VEGF); receptors for hormones or growth factors; an integrin; protein A or D; rheumatoid factors; a neurotrophic factor such as bone-derived neurotrophic factor (BDNF), neurotrophin-3, -4, -5, or -6 (NT-3, NT-4, NT-5, or NT-6), or a nerve growth factor such as NGF-β; platelet-derived growth factor (PDGF); fibroblast growth factor such as aFGF and bFGF; epidermal growth factor (EGF); transforming growth factor (TGF) such as TGF-α and TGF-β, including TGF-β1, TGF-β2, TGF-β3, TGF-β4, or TGF-β5; insulin-like growth factor-I and -II (IGF-I and IGF-II); des(1-3)-IGF-I (brain IGF-I); insulin-like growth factor binding proteins; CD proteins such as CD3, CD4, CD8, CD19 and CD20; erythropoietin (EPO); thrombopoietin (TPO); osteoinductive factors; immunotoxins; a bone morphogenetic protein (BMP); an interferon such as interferon-α, -β, and -.gamma.; colony stimulating factors (CSFs), e.g., M-CSF, GM-CSF, and G-CSF; interleukins (ILs), e.g., IL-1 to IL-10; superoxide dismutase; T-cell receptors; surface membrane proteins; decay accelerating factor (DAF); a viral antigen such as, for example, a portion of the AIDS envelope; transport proteins; homing receptors; addressins; regulatory proteins; immunoadhesins; antibodies; and biologically active fragments or variants of any of the above listed polypeptides.

Andya, col. 6, l. 45 to col. 7, l. 16. FSH is one protein on this broad list. However, only two proteins are exemplified: the antibodies anti-HER2 and anti-IgE.

A preservative is an **optional** excipient in the diluent used for reconstitution (Andya, column 17, line 29 to 37). Andya does not describe any stability effects of the preservative and later notes that "[t]he amount of

preservative is determined by assessing different preservative concentrations for compatibility with the protein and preservative efficacy testing." Andya, col. 17, ll. 32-34. Fourteen preservatives, including phenol, m-cresol, and benzyl alcohol, are listed for possible use. Benzyl alcohol is listed as preferred; it is the preservative used in the exemplified formulations of anti-HER2 and anti-IgE.

Andya is clearly directed to formulations of anti-HER2 and anti-IgE. The mere fact that Andya contains a list of proteins for possible use in its invention does not teach, motivate, or suggest to the person of skill in the art that all proteins in the list can be formulated as such, and that all of the optional excipients, including the preservatives listed, will yield a stable formulation with all of the proteins. The skilled person, with knowledge of the degradative effect of preservatives on proteins and the unpredictability as to working combinations, simply would have no expectation of success for each and every combination disclosed in Andya. *See* DeFelippis, para. 19. Thus, Andya lacks an expectation of success for combinations of FSH with a preservative selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, and mixtures thereof. Moreover, Andya lacks any teaching, motivation, or suggestion to combine it with Skrabanja and Keene.

The Instant Invention

In sharp contrast and most unexpectedly in view of the express teaching of Donaldson and the combined teachings of Keene, Skrabanja, and Andya, the **present inventors discovered that FSH could be formulated with phenol, m-cresol, p-cresol, o-cresol, and mixtures thereof**, and that stability can be maintained for an extended period (enabling more convenient reconstituted FSH products and solution FSH products). *See*, *inter alia*, in the instant application, Page 38, lines 1-7 and page 60, Table IX.

Combination of the Prior Art

The mere fact that references can be combined or modified does not render the resultant combination obvious unless the prior art also suggests the desirability of the combination. *In re Mills*, 916 F.2d 680, 16 USPQ2d 1430 (Fed. Cir. 1990), M.P.E.P. § 2143.01.

> To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations.

M.P.E.P. § 2143.

> A statement that modifications of the prior art to meet the claimed invention would have been "'**well within the ordinary skill of the art** at the time the claimed invention was made'" because the references relied upon teach that all aspects of the claimed invention were individually known in the art is **not sufficient to establish a *prima facie* case of obviousness without some objective reason to combine** the teachings of the references. *Ex parte Levengood*, 28 USPQ2d 1300 (Bd. Pat. App. & Inter. 1993). *See also In re Kotzab,* 217 F.3d 1365, 1371, 55 USPQ2d 1313, 1318 (Fed. Cir. 2000) (Court reversed obviousness rejection involving technologically simple concept because there was no finding as to the principle or specific understanding within the knowledge of a skilled artisan that would have motivated the skilled artisan to make the claimed invention); *Al-Site Corp. v. VSI Int'l Inc.*, 174 F.3d 1308, 50 USPQ2d 1161 (Fed. Cir. 1999) (The level of skill in the art cannot be relied upon to provide the suggestion to combine references.).

M.P.E.P. § 2143.01 (emphasis added).

Picking and choosing the prior art without any suggestion or motivation to do so has been admonished by the Federal Circuit. The court noted in *McGinley v. Franklin Sports Inc.*, 60 U.S.P.Q.2d 1001 (Fed. Cir. 2001):

> The genius of invention is often a combination of known elements which in hindsight seems preordained. To prevent hindsight invalidation of patent claims, the law requires some "teaching, suggestion or reason" to combine cited references. *Gambro Lundia AB v. Baxter Healthcare Corp.*, 110 F.3d 1573, 1579, 42 U.S.P.Q.2d 1378, 1383(Fed. Cir. 1997). When the art in question is relatively simple, as is the case here, the opportunity to judge by hindsight is particularly tempting. Consequently, the tests of whether to combine references need to be applied rigorously. [citations omitted]

None of the cited references provides any teaching, suggestion, or motivation to combine one with another. Keene merely provides the sequence of human FSH, and was cited by the Examiner for that purpose alone. Skrabanja provides a liquid FSH formulation, in the same concentration range as the instant application. It provides explicit detail of excipients to be added. Preservatives are not taught or even suggested in the specification. In fact, the examples demonstrate the stability of **unpreserved formulations** in cartridges for multiple use. Andya provides lyophilized formulations that can be reconstituted **to yield high concentration** liquid formulations, and then

exemplifies only two proteins in a list more than 100. Other than anti-HER2 and anti-IgE, no guidance is provided as to which proteins would work with which preservatives. A person of skill in the art would not expect that every protein on the list would yield a stable formulation if a preservative were added. *See* DeFelippis, para. 19.

The instant invention provides a pharmaceutically acceptable, solution formulation comprising human FSH and a preservative in an aqueous diluent, wherein (a) the preservative is selected from the group consisting of phenol, m-cresol, p-cresol, o-cresol, and benzyl alcohol, (b) the concentration of FSH is 5.0 μg/mL to 2 mg/mL, (c) the FSH consists of an α-subunit having SEQ ID NO:5 and a ß-subunit having SEQ ID NO:6, held together by noncovalent interactions, and (d) the formulation is suitable for multi-dose administration by injection. To arrive at this invention, the Examiner must specifically select FSH from the general and extensive list proteins in Andya, select the appropriate preservatives from another list of "optional" ingredients, disregard the high concentration of Andya and instead use the lower concentration disclosed in Skrabanja.

The Examiner states that motivation to combine the cited references comes from "knowledge generally available to one skilled in the art." Yet, this simply and improperly ignores the noted instability of FSH in the prior art (*see* DeFelippis, para. 11; Beals, para. 75-77), the long-felt need to improve FSH formulations (*see* Beals, para. 75; Plouffe, para. 7), the express and much more specific teaching of Donaldson (*supra*), and the prior attempts to stabilize FSH (*see* Moyle *et al.*, U.S. Pat. No. 5,508,261 (reference AB), which sought to improve the stability of FSH through preparation of analogs, Boime *et al.*, U.S. Pat. No. 6,638,890 (reference AU), which sought to improve stability by preparing single-chain monomers of glycoproteins, as opposed to non-covalently bonded heterodimers, and Skrabanja *et al.*, *supra*, which sought to improve stability by adding a thioether (*i.e.*, methionine)). Such unsupported justification is exactly the hindsight that the Federal Circuit admonished in *McGinley*. Only in hindsight does one skilled in the art pick and choose FSH from the long list of proteins described in Andya with the gonadotropins identified in Skrabanja and then pick and choose phenol or m-cresol from known preservatives listed in Andya. Moreover, even if one were to pick and choose FSH and a preservative of the instant invention, the inherent unpredictability in formulation chemistry does not provide the required expectation of success. As noted in REMINGTON'S PHARMACEUTICAL SCIENCES 1550 (Gennaro *et al.* eds., 1990), "Antimicrobial agents must be studied with respect to compatibility with all other components of the formula. In addition, their activity must be evaluated in the total

formula. It is not uncommon to find that a particular agent will be effective in one formulation but ineffective in another."

Protein-preservative compatibility is recognized as being unpredictable. *See* DeFelippis, para. 12-14. FSH, a complex heterodimer, was recognized as being susceptible to protein instability due to potential disruption in the noncovalent interactions that form the quaternary structure. *Id.* The perceived instability of the FSH heterodimer in the presence of a preservative was reinforced by the fact that FSH for use in humans had been sold only in lyophilized forms and only for single use for over 30 years. *See* Beals, para. 46. Thus, when read in context, neither Skrabanja, nor Andya, nor the general knowledge in the art provides any expectation of success. Accordingly, the Examiner's *prima facie* finding of obviousness is improper.

D. Secondary Considerations

Long-felt but unresolved need

The Declaration of Dr. Beals establishes the recognized instability of FSH (*see* para. 74-77) and demonstrates a long-felt need for improved formulations of FSH (*see* para. 46, 73, and 78-83). The declaration further notes that other gonadotropins, namely hCG, were formulated as preserved solutions with benzyl alcohol. Dr. Beals further established that, despite the fact that the nature of the usage of FSH products (daily treatment, over a period of about 10-14 days, with the need for typically 1-3 injections per day) made them ideally suited for multi-dose and despite the fact the means to create a multi-dose product were generally known, no pharmaceutical use multi-dose, preserved FSH products were available. The fact that a seemingly simple invention was at the fingertips of skilled artisans in the field, yet not discovered, is **powerful, contemporaneous evidence of non-obviousness**. Applicants therefore respectfully request that the Examiner review the evidence provided by Dr. Beals with respect to the recognized instability of FSH and the long-standing but unmet need for the present invention.

Commercial success

There can be no question that the use of benzyl alcohol has contributed to the commercial success of two products now commercially sold, PUREGON® brand FSH and GONAL-F® MULTI-DOSE brand FSH. Both products comprise human FSH and a preservative in an aqueous diluent, wherein (a) the preservative is benzyl alcohol, (b) the

concentration of FSH is 5.0 μg/mL to 2 mg/mL, (c) the FSH consists of an α-subunit having SEQ ID NO:5 and a β-subunit having SEQ ID NO:6, held together by noncovalent interactions, and (d) the formulation is suitable for multi-dose administration by injection.

Such products were introduced into the market in 2000 and 2001. Since introduction, GONAL-F® MULTI-DOSE brand FSH has garnered 15.7% of the US market, 25.2 % of the Canadian market and an average of 18.8% of the European market (ranging from 1.2% to 37.6%) by Q4-2002. PUREGON® has garnered 24.2% of the Canadian market and an average of 23.9% of the Europe market (ranging from 2.8% to 53.9%) in Q42002 (The US product, Follistim®-AQ was approved in 2004, and thus, US data are not available).

A review of Serono's website (http://www.seronofertility.com/to_ht_gonalF.jsp) makes clear that the success of GONAL-F® MULTI-DOSE is attributable at least in part to the use of benzyl alcohol thereby making the reconstituted formulation suitable for multi-dose administration. For example, the website provides:

> Gonal-f® is the most prescribed FSH in the US and in the world. It is the only FSH available in convenient multi-dose vials, offering several important benefits to patients:
>
> **Fewer Steps** Gonal-f® Multi-Dose comes with a pre-filled diluent syringe, eliminating the extra step of preparing a diluent syringe.
>
> **Less Mixing** Each Gonal-f® Multi-Dose vial contains as much medicine as 14 single dose vials or ampules of 75 IU each, so you only have to mix one time to have treatment prepared over several days. After reconstitution, the solution must be refrigerated.
>
> Patient-Preferred
> In a recent study, 96% of patients said Gonal-f® Multi-Dose was easy to handle, and 94% preferred the convenience of one-step reconstitution.[1]...
>
> [1] Hinrichsen MJ, Weise G. German Phase III open multicenter study to evaluate the convenience and safety of recombinant FSH injections supplied as 1200 IU multidose (Gonal-f® Multi-Dose) in ART cycles. ESHRE, June 2002.

With GONAL-F® brand FSH, FSH is sold as a lyophilized product and reconstituted in a diluent comprising benzyl alcohol so that the solution can be used over the course of therapy (up to 28 days).

PUREGON® is a solution product comprising FSH and benzyl alcohol. With regard to PUREGON®, which is now approved in the US as FOLLISTIM®, Organon, the manufacturer, stated:

> The U.S. Food and Drug Administration (FDA) today announced approval of Follistim®-AQ TM cartridge (follitropin beta injection) in the United States. Follistim-AQ cartridge is the first follicle stimulating hormone (FSH) treatment available in a pre-filled, pre-mixed solution, eliminating the need for patients to mix one or more vials of medication. Follistim-AQ cartridge is designed to be used only with the Follistim Pen®, an innovative pen device that facilitates accurate delivery of individualized doses of pre-mixed follitropin beta injection, a highly effective and widely used prescription fertility medication. Follistim is prescribed for women undergoing assisted reproductive treatments (ART) such as in vitro fertilization (IVF), and for the induction of ovulation to achieve pregnancy. Follistim-AQ cartridge, used with the Follistim Pen, provides women with a discreet, convenient method to self-administer fertility treatment with ease and confidence using the unique dial-a-dose feature. Organon USA Inc. markets Follistim-AQ cartridge and Follistim Pen. In Europe it is marketed under the brand name PUREGON Pen®.

24 March 2004 *(Arnhem, The Netherlands).* Although not explicit in the press release, Follistim-AQ is a solution comprising FSH and benzyl alcohol so that the solution can be used over the course of therapy.

The commercial success of these products provides further evidence that the present invention provided a significant and nonobvious advance over the art and is therefore patentable.

Adoption by others in the field

Recently, Serono has been granted approval by the FDA to market a new formulation of FSH, Gonal-f® RFF Pen (RFF stands for revised formulation female). According to the information leaflet on http://www.fda.gov/cder/foi/label/2004/21684_gonal-f_lbl.pdf (reference CCD), the pen contains m-cresol as a preservative. **The NDA for this product was submitted 23 May 2003** (*see* letter to Ms. Pamela Williamson Joyce, reference CCE), **more than three years after the publication of the instant application** as WO 00/04913, **published 3 February 2000**. Adoption by others is further evidence of the nonobviousness of this product.

E. Summary

Applicants have presented compelling evidence demonstrating:

(1) The clear disadvantages of a lyophilized protein product and the treatment regiment of FSH created a need to discover improved formulations of FSH (Beals, para. 78);

(2) FSH is a complex heterodimer and had been formulated as a lyophilized, single use product for over 30 years (Beals, para. 46);

(3) As a complex heterodimer, FSH was characterized in the art as being susceptible to protein instability (Beals, para. 74-77, and DeFelippis, para. 8, and citations therein);

(4) Despite the need, and the fact that related gonadotropin formulations were prepared with benzyl alcohol, FSH for use in humans had not been so formulated for the 30 years it had been on the market (Beals, para. 46);

(5) Protein-preservative compatibility is largely unpredictable. One skilled in the art would not have a reasonable expectation that any given preservative would be compatible with FSH (DeFelippis, para. 12-13);

(6) In view of the literature and product history, one skilled in the art would expect protein instability when formulating FSH with a preservative such as phenol, m-cresol, p-cresol, o-cresol, or mixtures thereof, at the time of invention (Beals, para. 76 and DeFelippis, para. 13);

(7) One skilled in the art would not interpret Skrabanja or Andya as suggesting the present invention or as providing a reasonable expectation of success (DeFelippis, para. 17-21);

(8) "General knowledge" in the field would not lead one skilled in the art to combine Skrabanja or Andya nor would it provide an expectation of success (DeFelippis, para. 13 and 22); and

(9) Products comprising human FSH and benzyl alcohol in an aqueous diluent were sold commercially in 2001 and have been commercially successful. A significant distinction between these products and prior products is the use of stable solutions of FSH and benzyl alcohol that enable multi-use, solution products.

In view of this evidence, argument, and the law, the obviousness rejection of Claims 158 and 159 is improper. Accordingly, Applicants respectfully request that the rejection be withdrawn so that the application can proceed to allowance without further delay.

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Rejection of Claims 159 and 160 Under the Doctrine of Double Patenting

Claims 159 and 160 stand "rejected under the judicially created doctrine of double patenting over 128 of copending Application No. 09/928,198." The new claims no longer contain benzyl alcohol as a preservative, thereby obviating the double patenting rejection. In light of this, the Applicants request that the Examiner withdraw the double patenting rejection.

Conclusion

The Applicants respectfully request that all rejections be removed from the current claims in light of the evidence, arguments, and law presented herein, and that the application be advanced to allowance.

Respectfully submitted,

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